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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
EPPERSON, JON D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 07/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/738,871	SHORT ET AL.	
	Examiner	Art Unit	
	Jon D Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *65-71* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *65-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/23/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. The Response filed May 10, 2004 is acknowledged.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of the Claims

3. Claims 1-72 were pending. Applicants canceled claims 1-64 and 72 and amended claim 56. Therefore, claims 65-71 are pending and examined on the merits.

Withdrawn Objections/Rejections

4. The Double Patenting Rejections with regard to U.S. Patent No. 6,174,673 are withdrawn in view of Applicants' submitted Terminal Disclaimer. The Double patenting rejections under 35 U.S.C. § 101 are withdrawn in view of Applicants' cancellation of claims and/or amendments. All other rejections are maintained and the arguments are addressed below.

Outstanding Objections and/or Rejections

Claim Rejections - 35 USC § 112

5. Claims 65-71 are rejected under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 USC 112, ¶ 1 "Written Description" Requirement, Federal

Register, Vol. 66, No. 4 pages 1099-1111, Friday January 5, 2001. This is a written description rejection.

These claims encompass a broad genus. For example, claims 65-71 outline method steps for obtaining an organism from a mixed population of organisms by encapsulating at least one of said microorganisms in a microenvironment and separating said microorganism by flow cytometry. The specification and claims do not place any limit on the number of atoms, the types of atoms, or the manner in which said atoms might be connected to form the microenvironment. This reads on an infinite number of possibilities and thus represents enormous scope. Furthermore, Applicants have not provided any common attributes that can link together ***all*** of these potential "microenvironments" i.e., there is no teaching that would allow a person of skill in the art to determine *a priori* ***all*** the different types of compounds that should be included in this enormous genus from the few examples provide by applicants. Furthermore, the specification only teaches "microorganisms" and, as a result, Applicants are not is possession of the broader organisms that are not microorganisms.

The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify ***all*** of the members of the genus or even a substantial portion thereof, and because the genus is enormous and highly variant, listing examples that are known in the art like gel microdroplets (e.g., Applicants' elected species, see also 35 U.S.C. § 102 rejections below) is insufficient to teach the entire genus. Consequently, one of skill in the art would reasonably conclude that the disclosure fails to

provide a representative number of species to describe this enormous genus. Thus, applicant was not in possession of the claimed genus.

With respect to adequate disclosure Applicant is referred to the discussion in *University of California v. Eli Lilly and Co.* (U.S. Court of Appeals Federal Circuit (CAFC) 43 USPQ2d 1398 7/22/1997 Decided July 22, 1997; No. 96-1175) regarding disclosure. For adequate disclosure, like enablement, requires *representative examples* which provide reasonable assurance to one skilled in the art that the compounds falling within the scope both possess the alleged utility and additionally demonstrate that *applicant had possession of the full scope of the claimed invention.* See *In re Riat*_(CCPA 1964) 327 F2d 685, 140 USPQ 471; *In re Barr* (CCPA 1971) 444 F 2d 349, 151 USPQ 724 (for enablement) and University *of California v. Eli Lilly and Co* cited above (for disclosure). The more unpredictable the art the greater the showing required (e.g. by "representative examples") for both enablement and adequate disclosure. Here, Applicants have not provided enough examples to show that they were in possession of the broad claims (see above).

Response

6. Applicant's arguments directed to the above written description rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue that a written description rejection should not be applied to method claims (e.g., see 5/10/2004 Response, page 5, second paragraph, "Applicants respectfully submit that the analogy of a method claim to a chemical compound ... is not apt").

[2] Applicants argue that the specification provides a "plethora" of examples that adequately describe the invention and cite pages 23-25 (microenvironments) and page 34 (mixed populations of organisms) and page 9 (markers) of the specification in support of this position (e.g., see 5/10/2004 Response, pages 6-7).

This is not found persuasive for the following reasons:

[1] Examiner contends that "method claims" also must be adequately described (e.g., see *Univ. of Rochester v. G.D. Searle & Co.*, 249 F. Supp. 2d 216, 228 (W.D.N.Y. 2003); affirmed by the CAFC on appeal, see *University of Rochester v. G.D. Searle & Co., Inc.*, 358 F.3d 916, 69 USPQ2d 1886 (Fed.Cir.2004)), wherein the court held that "Regardless whether a compound is claimed per se or a method is claimed that entails the use of the compound, the inventor cannot lay claim to that subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods. As the district court observed, '[t]he claimed method depends upon finding a compound that selectively inhibits PGHS-2 activity. Without such a compound, it is impossible to practice the claimed method of treatment.'") (emphasis added).

[2] First, the Examiner contends that Applicants have merely provided a "laundry list" of potential examples that are not adequately described (e.g., See, *Fujikawa v. Wattanasin*, 93 F.3d 1559,1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) (a "laundry list" disclosure of every

possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species).

In addition, the Examiner contends that the species disclosed in the cited references even if *assuming arguendo* that they were adequately described are not "representative" of the "enormous" scope of the claimed invention. Here, Applicant's claimed scope represents only an *invitation to experiment* regarding possible microenvironment, mixed population of organisms and markers, which read on an "infinite" number of possibilities. There is simply insufficient disclosure to justify this "enormous" scope. Furthermore, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus, which has not been done.

The Examiner also notes that the claimed invention is highly unpredictable because it reads on an "infinite" number of possibilities. Thus, there is a greater need for representative examples in an unpredictable art that are necessary to demonstrate that applicant had possession of the full scope of the claimed invention. See *In re Riat* (CCPA 1964) 327 F2d 685, 140 USPQ 471; *In re Barr* (CCPA 1971) 444 F 2d 349, 151 USPQ 724 (for enablement) and *University of California v. Eli Lilly and Co* cited above (for disclosure). The more unpredictable the art the greater the showing required (e.g. by "representative examples") for both enablement and adequate disclosure. Here, Applicants' specification provides only one working example of a library e.g., Zap-II library (e.g., see Examples in specification) and, as a result, does not meet the "heightened" written description requirement for an unpredictable art area.

Finally, the Examiner notes that an objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary

skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). The Examiner maintains because of the breadth of the claims, the unpredictability of the art and the lack of any working examples, the above standard is not met.

Accordingly, the written description rejection cited above is hereby maintained.

Claims Rejections - 35 U.S.C. 102

7. Claims 65-67 are rejected under 35 U.S.C. 102(b) as being anticipated by Powell et al. (Powell, K. T.; Weaver, J. C. "Gel microdroplets and flow cytometry: rapid determination of antibody secretion by individual cells within a cell population" *Biotechnology* **April 1990**, 8, 4, 333-337).

For ***claim 65***, Powell et al. (see entire document) disclose method steps for determining the secretion of biologically important macromolecules using gel microdroplets and flow cytometry (see Powell et al., entire document), which anticipates claim 65. For example, Powell et al. disclose **[a]** encapsulating two or more organisms obtained from the sample, each in a microenvironment suitable for growth of the organisms (e.g., see Powell et al., figure 1 showing "a process of capturing ... a single cell entrapped within a gel microdroplet"; see also page 334, column 2, paragraph 4 showing "preparations of agarose GMDs containing secreting cells (mouse hybridoma), non-producing cells (mouse masticytoma), or a mixed population of these cell"; see also

figure 2), **[b]** incubating the encapsulated two or more organisms under such conditions and for such a time to allow the two or more organisms to grow or proliferate (see Powell et al., page 334, Incubation and fluorescence immunoassay section showing incubation on "aqueous culture medium capable of supporting cell metabolism and secretion" for incubation periods that are as "little as eleven hours ... (slightly less than one doubling time)" wherein the cells grow and secrete products), **[c]** sorting the microenvironments by flow cytometry on the basis of growth of the organism to obtain an organism from the sample that grows under the conditions (see Powell et al., abstract stating "the method combined flow cytometry with gel microdroplets"; see also figures 2-3; see also figure 1, "In a sorting flow cytometer, the GMD fluorescence signal could also be used as the basis of sorting").

For ***claims 66-67***, Powell et al. states that a wide range of microorganisms can be used including *E. coli* and states that these can be from an environmental sample (see Powell et al., page 333, paragraph 1 stating "microorganisms were retained and accumulated within individual GMDs [i.e., Gel microdroplets]"; see also figure 1; see also page 336, Discussion section, first paragraph stating "GMDs can be made from many types of gel material, to provide biocompatability for cells, so that many types of cells may be used"; see also reference 7 showing *E. coli* as an Example. Please note: *E. coli* can be found in environmental soil samples).

Response

8. Applicant's arguments directed to the above 35 U.S.C. § 102 rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed

persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue that their claims "do not require secretion or production of any analyte as the basis of cell separation" which presumably distinguishes the prior art from the claimed invention because the claimed invention is based on "cell growth" (e.g., see 5/10/2004 Response, page 7).

[2] Applicants argue that Powell et al. fail to disclose "separat[ing] organisms that grow under the incubation conditions from cells that do not grow under the incubation conditions" (e.g., see 5/10/2004 Response, page 7, second to last paragraph).

[3] Applicants argue, "Powell et al. are concerned with using gel microdroplets and flow cytometry, not as an assay for organism growth, but to determine a product secreted from an organism, which product becomes the analyte" (e.g., 5/10/2004 Response, page 7, second to last paragraph).

This is not found persuasive for the following reasons:

[1] The Examiner contends that Applicants' use of "comprising" terminology does not preclude "secretion" or "production" of an analyte. Furthermore, Applicants claims are drawn to sorting the encapsulated two or more organisms "on the basis" of growth, which is broader than simply sorting on growth alone. Consequently, the Examiner contends that Applicants' current claims still read on "secretion" and "production" because these physiological processes are "based" on growth. As an example, the Examiner submits Gregory et al. which clearly shows that secretion and production of proteins depends on cell growth i.e., high levels are secreted

"just after" the lag phase of growth (e.g., see Gregory et al., abstract, "We found that as the cultures leave the lag phase, they secrete high levels of ... Dkk-1"). Please note that Gregory et al. is being provided for the sole purpose of refuting Applicants' arguments (Gregory, C. A.; Singh, H.; Perry, A. S.; Prockop, D. J. "The Wnt Signaling Inhibitor Dickkopf-1 Is Required for Reentry into the Cell Cycle of Human Adult Stem Cells from Bone Marrow" *J. Biol. Chem.* **2003**, 278 (30), 28067-28078).

[2] In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., separating organism that grow under the incubation conditions from cells that do not grow under the incubation conditions) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

[3] In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., an "assay") are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Accordingly, the 35 U.S.C. §102 rejection cited above is hereby maintained.

9. Claims 65-69 are rejected under 35 U.S.C. 102(b) as being anticipated by Weaver et al. (U.S. Patent No. 5,055,390) (Date of Patent is **October 8, 1991**).

For ***claim 65***, Weaver et al. (see entire document) disclose a process for the chemical manipulation of liquid and gel microdroplets, which anticipates the claimed invention. For example Weaver et al. disclose **[a]** encapsulating two or more organisms obtained from the sample, each in a microenvironment suitable for growth of the organisms (e.g., see Weaver et al., see Summary of the Invention; see also column 41, lines 33-35, "Specimens of GMDs [i.e., gel microdroplets] which contain one or more microorganisms are ... grow[n]"; see also column 47, Measurements of Mixed Biological Populations section, especially column 47, lines 51-66), **[b]** incubating the encapsulated two or more organisms under such conditions and for such a time to allow the two or more organisms to grow (see Weaver et al., column 31, Determination of Biological Growth section, see also column 41, lines 33-35, "Specimens of GMDs [i.e., gel microdroplets] which contain one or more microorganisms are ... grow[n]"; see also column 12, line 26; see also column 15, line 51; see also column 17, lines 25-35; see also column 17, lines 60-63, "Following an incubation, growth may occur and result in increases in size and number of cells, such that an individually occupied microdroplet subsequently contains progeny cells of the initial single cell"), **[c]** sorting the microenvironments by a flow cytometer on the basis of growth of the organism to obtain an organism from the sample that grows under the conditions (e.g., see Weaver et al., column 28, Capturing Molecules at Binding Sites in GMDs section; see also column 29, line 45, "sorting the GMDs by using a flow cytometer/cell sorter"; see also column 36, line 23).

For ***claims 66-67***, Weaver et al. disclose a mixed population of microorganism from the environment (see Weaver et al., column 47, Measurements of Mixed Biological Populations section; see also column 1, line 19; see also column 2, line 18; see also column 42, Enumeration of Viable Biological Entities section; see especially, column 53, lines 34-66).

For ***claims 68-69***, Weaver et al. disclose acid-producing microorganism e.g., acidophiles (see Weaver et al., column 5, lines 1-7, "allows detection of ... acid-producing microorganisms"; see also column 48, paragraph 2).

Response

10. Applicant's arguments directed to the above 35 U.S.C. § 102(b) rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue that their claims "do not require secretion or production of any analyte as the basis of cell separation" which presumably distinguishes the prior art from the claimed invention because the claimed invention is based on "cell growth" (e.g., see 5/10/2004 Response, page 8).

[2] Applicants argue that a "non-aqueous environments" are not suitable for growing microorganisms (e.g., see 5/10/2004 Response, page 8, last paragraph).

[3] Applicants argue that Weaver et al. fail to disclose "separat[ing] organisms that grow under the incubation conditions from cells that do not grow under the incubation conditions" (e.g., see 5/10/2004 Response, paragraph bridging pages 8-9).

[4] Applicants argue that Weaver fails to disclose any method for screening organisms for growth without rely on fusion of microdroplets in a non-aqueous environment (e.g., see 5/10/2004 Response, page 9, paragraph 1).

This is not found persuasive for the following reasons:

[1] The Examiner contends that Applicants' use of "comprising" terminology does not preclude "secretion" or "production" of an analyte. Furthermore, Applicants claims are drawn to sorting the encapsulated two or more organisms "on the basis" of growth, which is broader than simply sorting on growth alone. Consequently, the Examiner contends that Applicants' current claims still read on "secretion" and "production" because these physiological processes are "based" on growth. As an example, the Examiner submits Gregory et al. which clearly shows that secretion and production of proteins depends on cell growth i.e., high levels are secreted "just after" the lag phase of growth (e.g., see Gregory et al., abstract, "We found that as the cultures leave the lag phase, they secrete high levels of ... Dkk-1"). Please note that Gregory et al. is being provided for the sole purpose of refuting Applicants' arguments (Gregory, C. A.; Singh, H.; Perry, A. S.; Prockop, D. J. "The Wnt Signaling Inhibitor Dickkopf-1 Is Required for Reentry into the Cell Cycle of Human Adult Stem Cells from Bone Marrow" *J. Biol. Chem.* **2003**, 278 (30), 28067-28078).

[2] In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., non-aqueous

environment) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Here, Applicants' arguments are simply not commensurate in scope with the claims because the claims are not limited to "aqueous" environments.

[3] In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., separating organism that grow under the incubation conditions from cells that do not grow under the incubation conditions) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

[4] The Examiner argues that Applicants arguments are not commensurate in scope with the claims because Applicants' "comprising" terminology would not preclude the use of cell fusion or non-aqueous environments.

Accordingly, the 35 U.S.C. §102 rejection cited above is hereby maintained.

11. Claims 65-70 are rejected under 35 U.S.C. 102(e) as being anticipated by Thompson et al. (US Patent No. 5,824,485) (Filed **April 24, 1996**).

For ***claim 65***, Thompson et al. (see entire document) disclose a method for screening molecular diversity using encapsulation techniques with an expression library derived form a plurality of species of organisms, which anticipates claim 65.

For example, Thompson et al. disclose **[a]** encapsulating two or more organisms obtained from the sample, each in a microenvironment suitable for growth of the organisms (e.g., see Thompson et al., column 34, last paragraph, "The present invention also provides encapsulation as an efficient high-throughput method for growing cells in a confined space"; see also column 35, paragraph 1; see also section 5.2.3, especially column 37, lines 55-62, "Encapsulation may be performed in one of many ways, producing either macrodroplets (droplets from 0.5 to 2.5 mm) or microdroplets (droplets from 10 to 250 μm) depending upon the method of detection employed during subsequent pre-screening or screening. The size and the composition of the droplets may be controlled during formation of the droplets. Preferably, each macrodroplet or microdroplet will contain one to five library cells."). Thompson et al. also disclose **[b]** incubating the encapsulated two or more organisms under such conditions and for such a time to allow the two or more organisms to grow (e.g., see Thompson et al., column 39, line 29, "After a period of culturing, the positive cells may grow out of the droplet"; see also column 34, last paragraph). Finally, Thompson et al. disclose **[c]** sorting the microenvironments by a flow cytometer on the basis of growth of the organism to obtain an organism from the sample that grows under the conditions (e.g., see Thompson et al., column 33, lines 28-41, "The term 'pre-screen' refers to a general biological or biochemical assay which indicates the presence of an activity or compound ... The use of both pre-screens and screens generally embodies visual detection or automated image analysis ... fluorescence detection by fluorescence activated cell sorting (FACS) [i.e., flow cytometry]"; see also column 37, line 35; see also column 35, paragraph 2, column

36, paragraph 2; see more generally section 5.2.2.; see also column 47, paragraph 1-7; see also column 49, paragraph 2).

For ***claim 66***, Thompson et al. disclose an environmental sample (see Thompson et al., column 12, lines 38-44, "Any organism can be a donor organism for the purpose of preparing a combinatorial gene expression library of the invention ... from environmental samples either cultivable or uncultivable").

For ***claims 67-69***, Thompson et al. disclose thermophiles, acidophiles, halphiles (see Thompson et al., column 14, paragraph 1).

For ***claim 70***, Thompson et al. disclose fluorescence activated cell sorting (FACS), magnetic cell sorting (MACS), NMR (see Thompson et al., section 5.2.3, especially column 37, paragraph 3; see also column 47, line 50).

Response

12. Applicants' arguments directed to the above 35 U.S.C. § 102 rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue that Powell et al. fail to disclose "separat[ing] organisms that grow under the incubation conditions from cells that do not grow under the incubation conditions" (e.g., see 5/10/2004 Response, page 10, paragraph 1).

[2] Applicants argue that Thompson et al. describe screening "combinatorial gene libraries" in host organisms to determine a product secreted from a host organism and cite the office action at page 13 in support of this position (e.g., see 5/10/2004 Response, page 10, paragraph 1).

[3] Applicants argue that Thompson et al. are absolutely silent regarding use of gel microdroplets (or any other type of microenvironment) and flow cytometry as a means of sorting native organisms to distinguish between those that have grown during incubation in vitro from those that have not (e.g., see 5/10/2004 Response, page 10, paragraph 2).

This is not found persuasive for the following reasons:

[1] In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., separating organisms that grow under the incubation conditions from cells that do not grow under the incubation conditions) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

[2] The Examiner contends that Applicants' arguments are not commensurate in scope with the claims (i.e., the use of "comprising" terminology would not preclude the screening of "combinatorial gene libraries").

[3] In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., use of gel microdroplets (or any other type of microenvironment) and flow cytometry as a means of sorting native organisms to distinguish between those that have grown during incubation *in vitro* from

those that have not) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

In addition, the Examiner notes that Applicants' claims are drawn to sorting the encapsulated two or more organisms "on the basis" of growth, which is broader than simply sorting on growth alone. Consequently, Thompson et al. do recite each and every element of the claims. As an example, the Examiner submits Gregory et al. which clearly shows that secretion and production of proteins depends on cell growth i.e., high levels are secreted "just after" the lag phase of growth (e.g., see Gregory et al., abstract, "We found that as the cultures leave the lag phase, they secrete high levels of ... Dkk-1"). Please note that Gregory et al. is being provided for the sole purpose of refuting Applicants' arguments (Gregory, C. A.; Singh, H.; Perry, A. S.; Prockop, D. J. "The Wnt Signaling Inhibitor Dickkopf-1 Is Required for Reentry into the Cell Cycle of Human Adult Stem Cells from Bone Marrow" *J. Biol. Chem.* **2003**, 278 (30), 28067-28078).

Finally, the Examiner notes that both microdroplets and flow cytometry are disclosed by Thompson et al. (see rejection above).

Accordingly, the 35 U.S.C. § 102 rejection cited above is hereby maintained.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 65-71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thompson et al. (US Patent No. 5,824,485) (Filed **April 24, 1996**) and Kotitz et al. (Kotitz, R.; Bunte, T.; Weitschies, W.; Trahms, L. "Superconducting quantum interference device-based magnetic nanoparticle relaxation measurement as a novel tool for the binding specific detection of biological binding reactions" *J. Appl. Phys.* **15 April 1997**, 81, 8, 4317).

For ***claims 65-70***, Thompson et al. teaches all the limitations stated in the 35 U.S.C. 102(b) rejection above (incorporated in its entirety herein by reference), which anticipates claims 65-70 and, consequently, also renders obvious claims 65-70.

The prior art teaching of Thompson et al. differs from the claimed invention as follows:

For ***claim 71***, the prior art teachings of Thompson et al. differ from the claimed invention by not specifically reciting the use of a "Super Quantum Interference Device."

Thompson et al. is deficient in that it only teaches the use of fluorescence activated cell sorting (FACS), magnetic cell sorting (MACS), NMR (see Thompson et al., section 5.2.3, especially column 37, paragraph 3; see also column 47, line 50).

However, Kotitz et al. teaches the following limitations that are deficient in Thompson et al.:

For ***claim 71***, Kotitz et al. (see entire document) teaches the use of a super quantum interference device (SQUID) (see Kotitz et al., abstract).

It would have been obvious to one skilled in the art at the time the invention was made to use SQUID as taught by Kotitz et al. with the method of Thompson et al. because Kotitz et al. state that this technique is useful for detection of biological binding reactions and specifically points to antibody/antigen reactions (see title and abstract) that would include antibody/antigen reactions discussed by Thompson et al. (see column 32, line 63; see also column 35, lin24). Furthermore, one of ordinary skill in the art would have been motivated to use SQUID because Kotitz et al. explicitly states that the technique shows a "higher sensitivity" for these systems (see Kotitz et al., abstract). Furthermore, one of ordinary skill in the art would have reasonably expected to be successful because Kotitz et al. shows a successful example with an analogous system.

Response

16. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified

from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue that their remarks "regarding the failure of Thompson to disclose the invention methods apply equally and are incorporated here" (e.g., see 5/10/2004 Response, page 11, paragraph 1).

[2] Applicants argue, "Thompson's very emphasis upon chimeric engineered libraries and screening of transfected host cells on the basis of whether the organism secretes a product or interacts in some way with an introduced sequence would lead those of skill in the art away from the simplicity of screening encapsulated native organisms using flow cytometry on the basis of growth of the organism" (e.g., see 5/10/2004 Response, page 11, paragraph 1).

[3] Applicants argue, "there would be no reasonable expectation of success, especially with respect to organisms obtained from environmental samples. As Applicants teach in the Background of the Specification, most of such organisms have not been successfully cultured in vitro, thus providing those of skill in the art with doubt that a method along the lines of the invention could or would succeed" (e.g., see 5/10/2004 Response, page 11, paragraph 1).

[4] Applicants argue, "Kotitz et al. are silent regarding use of SQUID or any other type of magnetic field sensing device for flow cytometry screening to distinguish between microenvironments, such as gel microdroplets, containing organisms that have grown during incubation in a microenvironment and those containing organisms that did not grow under such conditions" (e.g., see 5/10/2004 Response, page 11, paragraph 1).

This is not found persuasive for the following reasons:

[1] The Examiner contends that Applicants arguments with respect to the Thompson et al. reference were adequately addressed above and are incorporated in their entirety herein by reference (e.g., see Thompson et al. rejection under 35 U.S.C. §102 and corresponding response to Applicants' arguments).

[2] The Examiner contends that Applicants' use of "comprising" terminology does not preclude "secretion" or "production" of an analyte or the use of "chimeric" engineered libraries. Furthermore, Applicants claims are drawn to sorting the encapsulated two or more organisms "on the basis" of growth, which is broader than simply sorting on growth alone. Consequently, the Examiner contends that Applicants' current claims still read on "secretion" and "production" because these physiological processes are "based" on growth. As an example, the Examiner submits Gregory et al. which clearly shows that secretion and production of proteins depends on cell growth i.e., high levels are secreted "just after" the lag phase of growth (e.g., see Gregory et al., abstract, "We found that as the cultures leave the lag phase, they secrete high levels of ... Dkk-1"). Please note that Gregory et al. is being provided for the sole purpose of refuting Applicants' arguments (Gregory, C. A.; Singh, H.; Perry, A. S.; Prockop, D. J. "The Wnt Signaling Inhibitor Dickkopf-1 Is Required for Reentry into the Cell Cycle of Human Adult Stem Cells from Bone Marrow" *J. Biol. Chem.* **2003**, 278 (30), 28067-28078).

[3] In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., environmental sample) is not recited in the rejected claim(s) i.e., claim 65. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

In addition, the Examiner contends that Applicants' arguments fail to appreciate the teachings of the Thompson et al. (e.g., see column 12, section 5.1, especially, lines 37-44, "Any organism can be a donor organism ... from environmental samples either cultivable or uncultivable").

[4] In response to applicant's arguments against the Kotitz et. al. reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

New Rejections

Claims Rejections - 35 U.S.C. 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

17. Claim 65 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed had possession of the claimed invention. This is a new matter rejection.

Claim(s) 65 was amended in 5/10/2004 Response. However, the Examiner cannot find support for Applicants' new "two or more organism" subgenus (e.g., see claim 65(a)). In addition, the Examiner cannot find support for sorting "on the basis of growth of the organism", which would include an indefinite number of sorting techniques (e.g., see 35 U.S.C. 112, second paragraph rejection below. If applicant believes this rejection is in error, applicant must disclose where in the specification support for this amendment can be found in accordance with MPEP 714.02.

Claims Rejections - 35 U.S.C. 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

18. Claims 65 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. For **claim 65**, the phrase "sorting the microenvironments by a flow cytometer on the basis of growth of the organism" is vague and indefinite in view of step (b) of claim 65. For example, Applicants' claim 65 step (b) requires that the organisms be given adequate time to "grow" and, as a result, at least to some extent the "sorting" must be based on growth because all of the cells were allowed to grow before they were sorted. Consequently, the metes and bounds of the claimed invention cannot be determined.

B. **Claim 65** recites the limitation "the organisms" and "the organism" in lines 5 and 10, respectively. There is insufficient antecedent basis for these limitations in the claim. The Examiner recommends "the two or more organisms."

Double Patenting – Non-statutory

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

19. Claims 65-69 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5 of copending Serial No. 10/145,281 of copending Application No. US 20030077677 A1 ('677).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examiner application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1986).

Although the conflicting claims are not identical, they are not patentably distinct from each other because, both patents contain overlapping embodiments (i.e., the overlap in scope). For example, both references disclose **[a]** a method for obtaining an organism from a mixed population of organisms in a sample (e.g., compare claim 1 preamble of '677 to claim 65 preamble in the present application), **[b]** encapsulating in a microenvironment an organism from the sample (see compare claim 1(a) of '677 to claim 65(a)), **[c]** incubating the encapsulated organisms under such conditions and for such a time to allow the organism to grow or proliferate (e.g., compare claim 1(b) of '677 to claim 1(b) of the present application) and **[d]** sorting the encapsulated organisms by flow cytometry to obtain an organism from the sample (e.g., compare claim 1(c) of '677 to claim 65(c) of the present application. In addition, both references recite the use of **[e]** environmental samples (e.g., compare claim 66 of the present application to claim 2 of '677), **[f]** microorganisms (e.g., compare claim 68 of the present application to claim 3 of '677) and **[g]** extremophiles including hyperthermophiles, psychrophiles, etc. (e.g., compare claim 69 of the present application to claim 5 of '677).

The claims of '677 differ from the current claims by not reciting "two or more organisms" (e.g., compare claim 1 of '677 to claim 65(a) wherein "at least one organism" is claimed in '677 instead of "two or more organisms") and not reciting sorting the microenvironments by a flow cytometer "on the basis of growth" of the organism (e.g., compare claim 1(c) of '677 to claim 65(c) wherein claim 1(c) of '677 only recites "sorting ... by flow cytometry", but does not explicitly recite "on the basis of growth").

However, it would have been obvious to use "two or more organisms" because the claim 1 preamble of '677 requires a "mixed" population of organisms (i.e., you can't have a "mixed" population of organisms unless you have "two or more" different organisms). Thus, using only one organism would be inconsistent with the purpose of the method. In addition, it would have been obvious to sort "on the basis of growth of the organism because the organisms are allowed to grow and/or proliferate in step (b) of claim 1 (i.e., steps 1(b) and (c) of '677 add up to claim 1(c) of claim 65 in the present application because the sorting must inherently be based on the growth of the organism (at least to some extent) because claim 1 (b) of '677 provides for such growth before the sorting step occurs). In addition, the metes and bounds of currently amended claim 65 is not clear (e.g., see 35 U.S.C. 112, second paragraph rejection below). A person of skill in the art would have been motivated to use "two or more organisms" and sorting "on the basis of growth" because these limitations are provided in claim 1 of '677 and represent a preferred embodiment.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

20. Claims 65-71 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5 of copending Serial No. 10/145,281 of copending Application No. US 20030077677 A1 ('677).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examiner application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been

obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1986).

Here, claims 1-5 of '677 (especially claim 1) recite the same method for obtaining an organism as that of the present invention (e.g., see above obviousness-type double patenting rejection above, which is incorporated in its entirety herein by reference). The method of claims 70-72 differs from claims 1-5 of '677 by not reciting the use of a Super Conducting Quantum Interference Device. Kotitz et al disclose the use of a Super Conducting Quantum Interference Device for biological binding reactions that would encompass the binding reactions disclosed by '677 and thus render it obvious to combine the references (i.e., the references represent analogous art). Furthermore, a person of skill in the art would have been motivated to combine it to modify the method of claims 1-5 of '677 (especially claims 1, 9) to use a Super Conducting Quantum Interference Device as taught by Kotitz et al because Kotitz et al explicitly states that it a "higher sensitivity" can be obtained (see Kotitz et al, abstract).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (571) 272-0811.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
July 24, 2004

BENNETT CELSA
PRIMARY EXAMINER